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PATENT
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No. 8038
Yen Choo et al.	Examiner: Wessendorf, T.
Application No.: 09/424,482	Technology Center/Art Unit: 1639
Filed: February 29, 2000	REPLY BRIEF
For: NUCLEIC ACID BINDING POLYPEPTIDE LIBRARY	

Mail Stop Appeal Brief
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This reply brief is submitted in response to the Examiner's answer mailed June 1, 2006

1. STATUS OF CLAIMS

Claims 1, 2, 6, 7 and 27-34 are pending. Claims 3-5 and 8-26 are canceled.

2. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

After withdrawal of the rejection of claim 7 under 35 USC 112, first paragraph and the rejection of claims 6 and 32 under 35 USC 112, second paragraph, the grounds of rejection requiring review on appeal are:

1. Whether claims 1-2, 6 and 27-34 comply with the written description requirement of 35 USC 112, first paragraph.

2. Whether claims 1-2, 6-7 and 27-34 would have been obvious under 35 USC 103 over Greisman et al., Science 275, 657-561 (1997) [Greisman] in view of Choo et al., Current Opinion in Biotechnology 6, 431-436 (1995) [Choo].

3. ARGUMENT

3.1 Claims 1-2, 6 and 27-34 comply with the written description requirement of 35 USC 112, first paragraph 112, first paragraph

At pp. 3-4 of the Examiner's answer, the Examiner alleges that the appealed claims (except for claim 7) are not supported, and notes that MPEP 714.02 requires appellant to identify support for the claim amendment in the specification. However, the Examiner does not in these remarks address the support appellant did identify in the specification at pp. 4-5 of the appeal brief (and previously in prosecution). Appellants further note that the Examiner's statement that "[c]laim 1 drawn to the randomization of amino acids at position 2 of a zinc finger (i.e., D, A, R, Q, H, K, S, N) in the context of co-randomization of each of the remaining positions...." (p. 3, last paragraph Examiner's answer) does not accurately reflect the claim language. Claim 1 requires co-randomization of position 2 and 6 of adjacent zinc fingers but does not necessarily require randomization of other positions. The Examiner's analogous remarks regarding claim 30 (p. 4, first paragraph, Examiner's answer) do no reflect that claim 30 also requires co-randomization of positions 2 and 6 of adjacent zinc fingers but not necessarily randomization of other positions.

At p. 6, second paragraph of the Examiner's answer, the Examiner alleges that that present claim 1 appears to be a subgenus of the original claim 1, and a species of the random residues as recited in claim 7. The Examiner appears to be implying that present claim 1 lacks support because it is intermediate in scope between original claims 1 and 7. Such a position does not address the additional support identified by appellant in the specification as discussed at pp. 4-5 of the appeal brief.

At p. 7, second paragraph and p.8 first paragraph of the Examiner's answer, the Examiner provides the following comments in reply to the support identified by appellants in the specification.

> In reply, the specification at page 8, line 26 up to page 9, line 10 states that at least a pair position (i.e., 2 and 6) be random residues. If the disclosure of the specific residues, as of the filing date, is only the preferred residues then, the as-filed specification does not also provide support for the other non-preferred residues comprised in said positions 2 and 6. It is of interest to note appellant's statement at p. 7 of the Brief which states "...a library in which positions 6 and 2 in adjacent fingers are simultaneously randomized..."
>
> The original disclosure does not only provide support for the claimed combination of a specific random residue at e.g., position 2 with the non-preferred random residues at e.g., position six. But also does not describe the amino acid different residues comprised in the non-preferred residues as of the filing date.

Insofar as these remarks can be understood, it appears that the Examiner is alleging that the specification discloses only preferred sets of residues for each recited amino acid position, without disclosing which residues are not preferred. However, such disclosure in fact corresponds to the recitations of the claims at issue. For example, independent claim 1 specifies preferred residues for position 2 but leaves the residues for position 6 open, not specifying either preferred or nonpreferred residues. Likewise, independent claim 30 specifies preferred residues for position 6 and leaves residues for position 2 open.

If the Examiner is suggesting that 35 USC 112, first paragraph requires that the specification explicitly list nonpreferred amino acids residues (i.e., residues other than those recited in the Markush groups listed at p. 11 of the specification), notwithstanding that the claims do not recite any nonpreferred residues, appellants disagree. It is common knowledge that there are twenty encoded amino acids. By listing a preferred Markush group of such amino acids, the skilled person knows without any explicit listing in the specification that the nonpreferred amino acids are the rest of the twenty amino acids. "The forced recitation of known sequences [here, amino acids] in patent disclosures would only add unnecessary bulk to the specification," *Falkner v. Inglis,* 79 USPQ2d 1001 (Fed. Cir. 2006).

In sum, it is respectfully submitted that the Examiner has not provided any reason to refute the explanation provided in the appeal brief as to why the specification provides written description for the present claims.

3.2 Claims 1-2, 6-7 and 27-34 Not Obvious Under 35 USC 103 over Greisman et al., Science 275, 657-561 (1997) [Greisman] in view of Choo et al., Current Opinion in Biotechnology 6, 431-436 (1995) [Choo]

At pp. 4-5 of the Examiner's answer, the Examiner repeats the rejection from previous office actions to which appellants have already responded in the appeal brief. No further comments are needed.

In the paragraph bridging pp. 9-10 of the answer, the Examiner alleges that Fig. 3A of Greisman shows the claimed libraries of zinc finger proteins. In reply, the zinc finger proteins whose sequences are shown in Fig. 3A of Greisman are not themselves a library of zinc finger proteins but rather eight individual clones from a library of zinc finger proteins (see, e.g., Greisman, p. 658, paragraph bridging cols. 1 and 2). The sequences depicted on paper are not themselves zinc finger proteins but rather representations of them. The actual physical zinc finger proteins existed as individual isolates and together with other zinc finger proteins as a large library, but not together as a library consisting only of the zinc finger proteins whose sequences are shown in Fig. 3A. The individual zinc finger proteins corresponding to the sequences shown in Fig. 3A were picked from a large library (see footnote 15 of Greisman indicating that, before selection, his phage display libraries have 10^8-10^9 members and after

selection have greater than 10^5 members). After picking the clones, the zinc finger proteins exist as individual isolates, not as a library. Before picking the clones, the zinc finger proteins are part of a large library. The diversity present in the eight sequences shown in Fig. 3A cannot be assumed to represent that present in the large library of which the clones having those sequences were previously a part.

Even if, contrary to the above, it were assumed that the sequences of zinc finger proteins shown in Fig. 3A of Greisman were a library of zinc finger proteins, the diversity required by claims 1 and 7 would still not be present. Claim 1 specifies inter alia that a library of zinc finger proteins in which randomization extends to cover at least positions 2 and 6 of adjacent fingers and that the randomization at position 2 is restricted to amino acids selected from the group D, A, R, Q, H, K, S and N. However, the randomization at position 2 is not so restricted in the zinc finger proteins shown in Fig. 3A. For example, position 2 of finger 1 contains a T in some of the sequences shown in Fig. 3A, a residue not allowed by the recited Markush group in claim 1. Similarly, position 2 of finger 2 also contains a T in some sequences. Position 2 of finger 3 contains a G in some sequences, another residue not allowed by the recited Markush group in claim 1. Accordingly, Fig. 3A does not show the limited randomization at position 2 required by claim 1. All claims depending from claim 1 are distinguished for at least the same reasons.

Claim 7 is distinguished for the same reasons as claim 1 and on additional grounds. Claim 7 specifies Markush groups of amino acids to which randomization is restricted for each of positions -1 to +6. Claim 7 also species that randomization is restricted so that the amino acids in the recited Markush groups *appear* at the given positions. For example, claim 7 requires that amino acids R, Q, H, N, D, A and T *appear* at position -1. By contrast, only Q is present at position -1 in fingers 1 and 2 of Fig. 3A of Greisman and only T at position -1 in finger 3. Claim 7 requires that amino acids S, R, K and N appear at position +1 and that randomization be restricted to these amino acids. By contrast, only amino acid K is present at position +1 in finger 1. In finger 2, amino acids Q, H, L, R and A are present at position +1;. thus, the required amino acids S, K and N are missing, and prohibited amino acids Q, H, L and A are present at this position. Amino acids L, H, and S appear at position +1 in finger 3. Thus,

required amino acids R, K and N are missing and prohibited amino acids L and H are present at this position. Similar differences (i.e., required amino acids absent and prohibited amino acids present) exist between the amino acids occupying other positions in Fig. 3A and the Markush groups specified in the claims.

The Examiner alleges that appellants' arguments in the appeal brief are not commensurate with the claims, which are directed to libraries rather than a method. However, as discussed above, claim 1 specifies a library in which "randomization extends to cover at least positions 6 and 2 of adjacent first and second fingers" and also requires that randomization at position 2 be limited to a designated Markush group of amino acids. As discussed above, these limitations distinguish over the sequences of zinc finger proteins of Fig. 3A of Greisman even assuming, contrary to appellants' position, that these sequences are considered to be a library. Claim 7 further specifies a library in which "the following amino acids appear at the given positions" followed by a table of positions with a Markush group of amino acids for each position. As discussed above, the amino acids occupying the various positions of the zinc fingers shown in Fig. 3A of Greisman bear no resemblance to those required to appear at those position by the Markush groups of claim 7.

Independent claim 30 is distinguished over Fig. 3A of Greisman at least because the sequences shown in Fig. 3A of Greisman are not themselves a library but those of individual clones from a library including many other zinc finger proteins. Although the eight sequences shown in Fig. 3A have two different residues at position 2 of finger 1 (T and N) and two different residues at position 6 of finger 2 (Q and A), two amino acids are not necessarily representative of the diversity present at those positions in the large library from which the clones were obtained. The library from which they were obtained was randomized with sixteen different amino acids at each randomized position (see footnote 15 of Greisman). Although the size of the library was reduced from 10^8-10^9 to about 10^5 by selection against a target, there is no reason to conclude that the ~10^5 member surviving selection all had position 6 of finger 2 occupied by the Q or A of the eight analyzed sequences of Fig. 3A rather than a different one of the sixteen amino acids present at position 6 in the original library.

At p. 10, second paragraph of the answer, the Examiner alleges that it would have been within the ordinary skill to pick and chose from the known available sixteen amino acids disclosed by Greisman, the ones that combine to form the instant library. However, "[t]hat which is within the capabilities of one skilled in the art is not synonymous with obviousness." *Ex parte Gerlach,* 212 USPQ 471 (Bd. App. 1980). An "assertion that one of ordinary skill in the relevant art would have been able to arrive at applicant's invention because he had the necessary skills to carry out the requisite process steps" is an "inappropriate standard for obviousness." *Orthokinetics Inc. vs. Safety Travel Chairs Inc.*, 1 USPQ2d 1081 (Fed. Cir. 1986). "The mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggested the desirability of the modification." *In re Fritch,* 23 USPQ2d 1780, 1784 (Fed. Cir. 1992). Here, the cited art does not suggest the desirability of the modification. To the contrary, as noted in the appeal brief, the art suggested that more than the sixteen amino acids used by Greisman, rather than fewer, would be desirable. A patent by Choo, US 6,007,988 (of record) also omitted four amino acids (thus using sixteen) and explained that the reason was to avoid stop codons ("T in the first base position is omitted in order to avoid stop codons, but this has the *unfortunate* effect that the codons for Trp, Phe, Tyr and Cys are not represented" (at col. 12, lines 24-27, emphasis supplied).

In the paragraph bridging pp. 11-12 of the Examiner's answer, the Examiner repeats her remarks from the final office action that neither claim 1 nor claim 30 restricts the sets of amino acids at positions 2 and 6. It is not disputed that claim 1 only requires limited randomization to a defined Markush group of amino acids be conducted at position 2 and claim 30 only requires limited randomization at position 6. However, for the reasons discussed at p. 10, first paragraph of the appeal brief, such is not detrimental to patentability. The Examiner has not addressed the substance of these remarks.

At p. 12 of the answer, the Examiner alleges (without citation) that optimization of a given parameter is within the ordinary skill in the art. Appellants assume that the Examiner is referring to cases such as *In re Aller,* 220 F.2d 454, 105 USPQ 233 (CCPA 1955) holding that, when the general conditions of a claim are disclosed in the prior art, it is not inventive to

discover the optimum or working ranges by routine experimentation. However, *In re Aller* involved the optimization of temperature and concentration of an acid for a chemical process when the prior art already taught one value of temperature and concentration of acid that were effective. Both temperature and concentration of an acid are continuously varying linear parameters that can be easily be optimized by interpolation from a few data points. For example, if a process works well at 100 degrees and poorly at 50 degrees and 150 degrees, one can reasonably conclude that 100 degrees is near the optimum. By contrast, selection of subsets of amino acids for randomization to produce a library of zinc finger protein is not a continuous linear parameter that allows simple interpolations. Each of the amino acids is different, and the effect of its presence or absence at a given zinc finger position on the binding characteristics of a library of zinc finger proteins was unpredictable. Thus, selection of a set of amino acids to improve binding characteristics of a zinc finger protein library is not comparable to selecting a temperature or concentration of acid to conduct a chemical process.

Moreover, a prima facie case of obviousness based on optimization of ranges can be rebutted by showing that the art in any material respect teaches away from the claimed invention (*In re Geisler,* 43 USPQ2d 1362, 1366 (Fed. Cir. 1997)). Here, as discussed above, the art teaches that more different amino acids than were used by Greisman, not fewer (as claimed), would be desirable. The suggestion that more rather than fewer amino acids are desirable would have taught away from selecting a subset of the sixteen amino acids of Greisman.

In section 7.3.5 of the appeal brief, appellants provide several additional grounds of patentability for dependent claims 27, 28, 29, 33 and 34. These have not been addressed in the Examiner's answer. In the present reply brief, appellants have also provided additional grounds to distinguish claim 7.

4. CONCLUSION

For these reasons as well as the reasons provided in the appeal brief, it is respectfully submitted that the rejection should be reversed.

Respectfully submitted,

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